(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification[7]:   A61B 18/20

(21) International Application Number: PCT/US01/06061

(22) International Filing Date: 26 February 2001 (26.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/538,787   30 March 2000 (30.03.2000)   US

(71) Applicant: COHERENT, INC. [US/US]; 5100 Patrick Henry Drive, Santa Clara, CA 95054 (US).

(72) Inventors: FRANGINEAS, George; 2571 Ocala Street, Fremont, CA 94544 (US). PUMMER, Herbert; 347-23rd Street, San Mateo, CA 94430 (US). BLACK, John, F.; 2276 Allegheny Way, San Mateo, CA 94402 (US).

(74) Agent: STALLMAN, Michael, A.; Stallman & Pollock L.L.P., Suite 290, 121 Spear Street, San Francisco, CA 94105 (US).

(81) Designated State (national): JP.

(84) Designated States (regional): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DUAL-WAVELENGTH LASER-TREATMENT OF VASCULAR DISORDERS
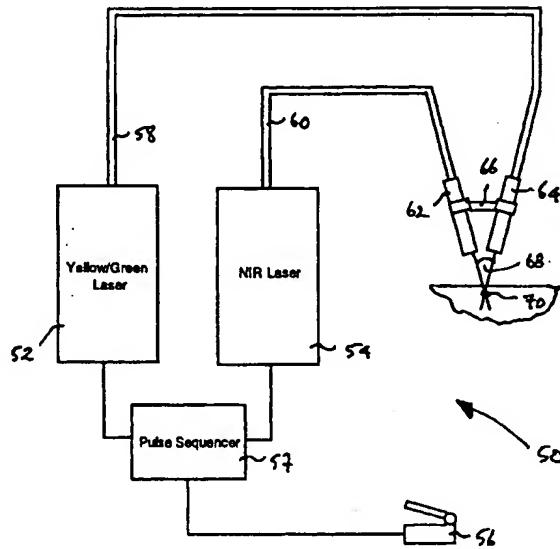
(57) Abstract: A method for treating vascular disorders includes irradiating an abnormal blood vessel with two pulses of electromagnetic radiation. One of the pulses has a longer wavelength than the other. The longer wavelength pulse is delivered concurrently with or at a relatively short time interval after the shorter wavelength pulse. Neither pulse delivers sufficient fluence to permanently damage the vessel if used alone. When the pulses are used in combination, the vessel is transformed by the shorter wavelength pulse to a condition where coagulation of blood in the vessel and permanent damage to the vessel can be caused by the second pulse.

WO 01/74265 A1

DUAL-WAVELENGTH LASER-TREATMENT OF VASCULAR DISORDERS

BACKGROUND OF THE INVENTION

TECHNICAL FIELD OF THE INVENTION

5   The present invention relates in general to laser treatment methods for vascular disorders. It relates in particular to the laser treatment of abnormal leg veins or telangiectasia.

DISCUSSION OF BACKGROUND ART

10   In recent years, use of lasers for treatment of vascular disorders has rapidly gained acceptance by the medical community. Lasers delivering light in the green and yellow regions of the visible spectrum are now effectively used to treat vascular disorders involving very small blood vessels, for example, the birthmark condition commonly referred to

15   as a port wine stain. The green and yellow wavelengths between about 530 and 590 nanometers (nm) are particularly favored because absorption of these wavelengths in blood hemoglobin is significantly higher than in the skin pigment melanin. This allows the hemoglobin to be selectively targeted by the radiation in a treatment often referred to

20   as selective photothermolysis. In such a treatment, blood in targeted vessels is coagulated by heat generated when the green or yellow light is absorbed in the blood hemoglobin. This results in necrosis of the vessels in the treated area. The coagulated or necrotized vessels are eventually reabsorbed by the body and replaced with scar tissue.

25   The treatment of such vascular disorders involving small blood vessels, for example about 200 to 1000 micrometers (µm) in diameter, is relatively well understood and practiced relatively problem free. Laser treatment of larger abnormal leg veins or telangiectases, however, continues to present problems in finding an effective laser treatment

method. The laser treatment of leg veins is inherently more difficult than the treatment of the facial veins of the port wine stain. This is due, inter alia, to the veins involved being generally larger, for example from about 1000 μm up to about 3.0 millimeters (mm) in diameter.

5   It is generally believed that leg veins can be eradicated only if the selected damage process reaches most of the circumference of the vein. One possible explanation for this may be because abnormal leg veins often have elevated hydrostatic pressure, which may counteract the effects of any less-than-complete vascular damage by restoring blood
10   circulation.

Attempting to coagulate larger vessels using green or yellow radiation in extended exposures or higher intensity exposures has been only partially successful and can lead to complications including scarring, scabbing, edema and epidermal damage or extravasation of red blood
15   cells from a vessel being treated. Extravasation can lead to formation of progressive purpura which are generally cosmetically unacceptable to patients. This has restricted treatments to date primarily to laser wavelengths in the near infrared (NIR) region of the spectrum. As these wavelengths are less effectively absorbed in blood, relatively high
20   fluence, for example, on the order of about 100 Joules per square centimeter (J/cm^2), is required. This often results in a patient feeling pain in the region being treated. This is believed to be due to diffusion of heat from the vessel to adjacent tissue including pain sensors.

There is a need for a laser treatment of leg veins which is able to
25   effectively destroy even the largest abnormal vessels involved. The method should be operable with the minimum of discomfort to the patient and without lasting, if any, cosmetic side-effects.

SUMMARY OF THE INVENTION

The present invention is directed to a method and apparatus for treating vascular disorders with electromagnetic radiation. In one aspect, the method of the present invention comprises delivering to a blood

5   vessel a first fluence of electromagnetic radiation having a first wavelength and a second fluence of electromagnetic radiation having a second wavelength. The second wavelength is longer than the first wavelength. The fluences are delivered in a manner such that they cooperatively cause permanent damage to the blood vessel.

10   In another aspect of the method of the present invention, delivery of the first fluence to the blood vessel causes one or more of shrinkage of the blood vessel, heating of blood in the blood vessel to a temperature above normal blood temperature, and partial blockage of the blood vessel by partially coagulating blood therein. The second fluence causes

15   complete coagulation of blood in the blood vessel. This contributes to causing the permanent damage.

In yet another aspect of the method of the present invention, the first fluence alone is not sufficient to cause complete coagulation of blood in the blood vessel, and completion of coagulation can be completed by a

20   second fluence less than that which would be necessary to complete coagulation of blood in the blood vessel in the absence of the first fluence.

Preferably, the first electromagnetic radiation fluence is provided by a first pulse of laser radiation having a wavelength between about 480

25   nm and 600 nm and the second fluence is provided by a second pulse of laser radiation having a wavelength between about 605 nm and 1350 nm. The pulses are preferably delivered sequentially, with the second pulse being delivered within a time interval less than twice the thermal relaxation time of the blood vessel.

Experimental irradiations of vessels of laboratory animals were performed, wherein the first pulse had a wavelength of 532 nm and the second pulse had a wavelength of about 1064 nm. There was a time delay of about 1.0 ms between the end of the first pulse and the

5   beginning of the second pulse. Permanent damage was caused to the vessels even though the fluence of the first and second pulses was respectively about one-half or less and one-third or less than would be required if a pulse or pulses of only one or the other wavelength were used. It is believed that the reduced fluences will provide for a vascular

10   disorder treatment method in which the possibility of pain or collateral damage to other tissues is significantly reduced.

Apparatus for carrying out the method of the present invention includes a first light-source for delivering electromagnetic radiation having the first wavelength and a second light-source for delivering

15   electromagnetic radiation having the second wavelength. A control arrangement is provided for controlling parameters of the electromagnetic radiation delivered by each of the first and second light-sources. The control arrangement includes a sequencer for timing cooperative activation of the first and second light-sources. An optical

20   arrangement is provided for delivering the electromagnetic radiation from each of the first and second sources to the blood vessel. The first and second light sources are preferably solid-state lasers.

In one preferred embodiment the first light-source is a pulsed, frequency-doubled Nd:YAG laser delivering pulses having a wavelength of

25   about 532 nm. The second light- source is a pulsed Nd:YAG laser delivering pulses having a wavelength of about 1064 nm. The optical delivery arrangement includes optical-fiber delivery.

BRIEF DESCRIPTION OF THE DRAWINGS

-5-

The accompanying drawings, which are incorporated in and constitute a part of the specification, schematically illustrate a preferred embodiment of the present invention, and together with the general description given above and the detailed description of the preferred
5   embodiment given below, serve to explain the principles of the invention.

FIG. 1 is a graph schematically illustrating diffusion of heat as a function of time from a blood vessel heated by NIR laser radiation.

FIG. 2 is a graph schematically illustrating diffusion of heat as a
10   function of time from a blood vessel heated by yellow-green laser radiation.

FIG. 3 is a transverse cross-section view schematically illustrating blood coagulation in a large blood vessel irradiated by yellow-green
15   radiation.

FIG. 4 is a longitudinal cross-section view schematically illustrating blood coagulation in a large blood vessel irradiated by yellow-green radiation and stenosis of the blood vessel in reaction to the coagulation.
20

FIGS 5A-C are graphs schematically illustrating a preferred delivery sequence of yellow-green and NIR radiation pulses in accordance with the method of the present invention.

25   FIG. 6 schematically illustrates one preferred apparatus for simultaneously or sequentially delivering yellow-green and NIR laser pulses in accordance with method of the present invention, with pulses being delivered along separate paths to a targeted blood vessel.

-6-

FIG. 7 schematically illustrates another preferred apparatus for simultaneously or sequentially delivering yellow green and NIR laser pulses in accordance with the present invention with pulses being delivered along separate paths to a targeted blood vessel.

5

FIG. 8 schematically illustrates yet another preferred apparatus for simultaneously of sequentially delivering yellow green and NIR laser pulses in accordance with the present invention with pulses being delivered along a common optical-fiber to a targeted blood vessel.

10

FIG. 9 is a graph schematically illustrating results of experimental, two-pulse irradiations in accordance with the method of the present invention on blood vessels of laboratory animals.

15   FIGS 10A-C are graphs schematically representing alternate delivery sequences of yellow-green and NIR pulses in accordance with the present invention.

DETAILED DESCRIPTION OF THE INVENTION

20   In order to highlight differences in the vascular disorder treatment method of the present invention from prior-art methods, a brief description of above-discussed limitations of yellow-green irradiation of blood vessels and NIR irradiation of blood vessels individually is first presented. These limitations include the possibility of pain accompanying

25   treatment in the case of near infrared irradiation, and the ineffectiveness of yellow-green irradiation on larger blood vessels. It should be noted here that the terminology yellow-green is used herein for convenience (rather than to ascribe actual colors to specific wavelengths) to collectively define those wavelengths in a range between about 480 and

30   600 nm. Similarly, the terminology NIR is used for convenience to

collectively define those wavelengths in a range between about 605 and 1350 nm, even though there is some overlap into the red region of the visible spectrum.

5   FIG. 1 graphically, schematically illustrates calculated heat distribution as a function of time in a blood vessel heated by a pulse of NIR radiation. The vertical (Y) axis is assumed to be the center of the vessel and vertical line A is assumed to be the vessel wall. Vertical line B situated 100 μm from the vessel wall is assumed to be the position of a nerve relative to the vessel. The base temperature is assumed to be the

10   normal body (blood) temperature of 37°C. Horizontal dotted line C represents a critical temperature of about 55°C above which nerve B will begin to sense pain.

Curves D1, D2, D3, D4, D5 and D6 schematically represent the temperature of blood in the vessel at respectively 100.0 microseconds

15   (μs), 1.0 milliseconds (ms) 10.0 ms, 100.0, ms, 1.0 second and 10.0 seconds after an irradiation pulse has heated the blood to a maximum temperature of about 90.0°C, which is about the temperature required to cause coagulation. The low absorption of blood for the NIR radiation permits a relatively uniform heating of all blood in the vessel, a

20   characteristic which, as discussed above, has made it attractive for treatment of larger vessels.

It should be noted here that the curves of FIG. 1 are computed based on certain assumptions made for convenience of calculation and should not be interpreted as giving a precise indication of blood

25   temperature at a given time. It is believed, however, that these curves represent the thermal dynamics of blood heating sufficiently for understanding a basic mechanism thereof.

Curves D1-6, collectively, schematically illustrate thermal diffusion of heat from the vessel into surrounding tissue, with temperature in the

30   vessel falling and temperature in surrounding tissue rising until an

equilibrium is reached at about 10.0 seconds after irradiation. From Curve D4 it can be seen that, in the hypothetical model of FIG. 1, the temperature of nerve B rises above the critical (pain) temperature C about 100.0 ms after the irradiation. From curves D5 and D6 it can be

5   seen that nerve B remains above the critical temperature for a time between about 1.0 and 10.0 seconds.

FIG. 2 graphically, schematically illustrates calculated heat distribution as a function of time in a blood vessel heated by a pulse of yellow-green radiation. The graphical axes and the position of vessel-

10   wall A and nerve B are as described above with reference to FIG. 1.

Curves E1, E2, E3, E4, E5 and E6 schematically represent the temperature of blood in the vessel at respectively 1.0 μs, 10.0 μs, 100.0 μs, 1.0 ms, 10.0 ms and 100.0, ms, after an irradiation pulse has heated the blood to the coagulation temperature of about 90.0°C. The

15   high absorption of blood for the yellow-green radiation causes initial heating and coagulation of the blood to be confined to a depth of about 50 μm in the vessel. Curves E1-6, collectively, schematically illustrate thermal diffusion of heat from the heated portion of the vessel. It can be seen that as a result of the restricted heating volume in the vessel, the

20   temperature at vessel-wall A and accordingly at nerve B, never exceeds the pain-threshold temperature (dotted line C).

It is pointed out here that the calculations of FIGS 1 and 2 assume, for simplicity of calculation, a radially symmetrical distribution of temperature from the center of the vessel. In reality, irradiation of the

25   vessels causing the heating will come from a particular direction. In the FIG. 1 case, because of the relatively uniform penetration, this "cross-section" representation is believed to provide a reasonable representation of temperature distribution anywhere around a vessel. In FIG. 2, the condition near the Y-axis more accurately represents the condition at that

30   part of the vessel wall on which the radiation is incident. Nevertheless, it

-9-

can be seen from curve E5 that the temperature is likely to fall below the pain-threshold temperature within 100.0 μm of the hottest part of the vessel, thereby reducing the chance of pain being felt by a nerve near the hottest part of the wall.

5   Referring now to FIG. 3, a shortcoming of yellow- green radiation in coagulating blood in a relatively large (0.5 to 1.0 mm) blood vessel is next discussed. Yellow-green radiation 20 is incident on epidermis 22 and is scattered on penetrating the epidermis forming an expanding beam as indicated by arcs 20A. The expanding beam penetrates a

10   melanin-rich region 24 at the base of the epidermis, penetrates dermis 26, and is incident on blood vessel 28.

           As noted above, the yellow-green radiation is strongly absorbed by . hemoglobin in blood in the vessel, thereby heating the blood and causing the blood to coagulate. Because of the high absorption in the

15   hemoglobin, the penetration depth is short compared with the diameter of the blood vessel. This causes coagulum 30 to form in the vessel. The coagulum has an even higher absorption (attenuation) for the radiation than uncoagulated blood and effectively shields the remaining blood 32 from radiation. The temperature of the remaining blood will increase via

20   heat diffusion from the coagulum but may remain below the temperature required for coagulation.

           Once the coagulum has formed, extending the exposure of the vessel to the radiation by means of a longer pulse or multiple pulses, or increasing the intensity of radiation are essentially ineffective in causing

25   coagulation to progress. Further, increasing the duration or intensity of the radiation can heat the coagulum above the boiling point of blood, leading to microvaporization of the blood. This can cause and expulsion (extravasation) of blood from the vessel, through vessel wall 34, into surrounding tissue with an attendant possibility of formation of purpura.

-10-

In addition to the formation of the coagulum 30, blood vessel 28 undergoes other changes in response to the yellow-green irradiation. These changes are important in the method of the present and a detailed discussion of these changes is set forth below.

5   It has been observed in experiments on samples of the skin of laboratory animals that on irradiation of a blood vessel by yellow-green light not only does coagulum form in response to the irradiation, but the vessel undergoes stenosis or shrinkage in the irradiated portion thereof. It is not known precisely how quickly the reaction occurs following the

10   radiation. In video monitoring of the irradiation it was observed to occur in less than a frame-repetition interval at a rate of thirty frames per second.

The situation following stenosis is depicted schematically in FIG. 4. Here, blood vessel 28 of FIG. 3 is depicted in longitudinal cross-section.

15   Vessel-wall 34 in the region of the vessel irradiated by scattered yellow-green radiation 20A has been reduced to about one-half of its original diameter indicated by dotted lines 34A. As a result of the shrinkage, the volume of uncoagulated blood in the irradiated area is reduced. By way of example, for a factor-of-two diameter shrinkage, the volume would be

20   reduced by about a factor of four compared with the volume prior to the shrinkage.

In the method of the present invention, the vessel is irradiated with NIR radiation to complete the coagulation initiated by the yellow-green irradiation. This is done either concurrently with the irradiation of

25   blood vessel 28 with yellow-green, or at some interval thereafter, preferably while blood in the vessel is still heated above its normal temperature. As the NIR radiation is not scattered to the extent of the yellow-green radiation in the epidermis and dermis, the NIR radiation can relatively precisely target the yellow-green irradiated area. Even though

30   the absorption coefficient for NIR radiation may be increased in coagulum

-11-

30, penetration of the entire vessel by the NIR radiation is still possible. Further, the absorption coefficient of the NIR for heated but uncoagulated blood in the vessel has been found to be higher than for unheated blood, by a factor of up to about four or five. This provides

5   that the heated blood can be more efficiently heated by the NIR radiation to complete the coagulation. It is believed, without being limited to a particular theory that the increased absorption results from a photoconversion from oxyhemoglobin (in normally flowing blood that has not been irradiated) to methemoglobin, the latter having a higher

10   absorption for NIR wavelengths than the former.

It is believed that a reduced volume of blood to be heated or a higher efficiency of heating blood, alone or in combination, is responsible for providing that the NIR radiation fluence required to complete coagulation is about one-third or less of that which would be required to

15   complete coagulation if the vessel were not stenosed. Reduced NIR fluence can contribute to a significant reduction in the possibility of pain being felt as a result of the inventive treatment. It is also believed that the stenosis and resultant reduction of blood volume by the yellow-green irradiation may somewhat more effective in reducing the required NIR

20   fluence than the pre-coagulation. This can allow use of a significantly lower yellow-green radiation fluence than would be required for vessel treatment using yellow-green radiation alone.

A preferred timing of radiation delivery in the method of the present invention is next discussed with reference to FIGS 5A, 5B and 5C.

25   Here, a pulse 40 of yellow-green radiation is delivered to a vessel being treated (see FIG. 5A). Preferably the radiation is delivered from a source of narrow spectral linewidth radiation such as a laser, or a gas discharge lamp. The radiation preferably has a wavelength between about 480 and 600 nm and most preferably between about 530 and 590 nm.

30   Preferably, pulse 40 has a duration T_G between about 2.0 ms and 100

-12-

ms. Pulse 40 may be delivered as a single continuous pulse or as a burst of shorter, higher-intensity pulses with the burst of pulses having a duration comparable to duration of the single continuous pulse. The total fluence in the pulse 40 or a burst equivalent thereof is preferably
5   between about 8.0 J/cm^2 and 30.0 J/cm^2.

Concurrently with or at some time interval ΔT following the termination of pulse 40, a pulse 42 of NIR radiation is delivered to a vessel being treated (see FIG. 5B). Here again, the radiation is preferably delivered from a laser or a gas-discharge lamp. The NIR
10   radiation preferably has a wavelength between 605 and 1350 nm and most preferably between about 605 and 1100 nm. One possible suitable wavelength is about 640 nm. This is a wavelength about which methemoglobin has an absorption peak. Preferably, pulse 42 has a duration T_{NIR} between about 2.0 ms and 100.0 ms. Pulse 42 may also be
15   delivered as a single, continuous pulse or a sequence of pulses as discussed above. The total fluence in pulse 42 or a sequence of such pulses is preferably between about 10.0 J/cm^2 and 100.0 J/cm^2 and most preferably between about 20 and 80 J/cm^2.

The interval ΔT between pulses 40 and 42 is preferably no longer
20   than about two thermal relaxation times for the vessel being treated. As is known in the art, the thermal relaxation time of a vessel is proportional to the square of the diameter of the vessel. By way of example, relaxation times for vessels of about 0.5 mm and 2.0 mm in diameter are about 75.0 ms and 1200.0 ms respectively. It is believed that in order to
25   achieve an optimum synergistic effect of the two different-wavelength pulses of the present invention, the vessel temperature at the instant of delivery of pulse 42 should preferably still be above the normal temperature of about 37° C as depicted in FIG. 5C. By way of example, an interval ΔT of about 100.0 ms or less is believed to be suitable for
30   vessels having a diameter of about 1.0 mm or less.

-13-

As noted above, pulses 40 and 42 may be delivered simultaneously consistent with the method of the present invention. Indeed, delivery of pulse 42 may even be initiated before pulse 40 provided there is sufficient overlap of the pulses for a synergistic effect to

5   result. Such temporal arrangements of the pulses are possible when pulse 42 provides a fluence less than would be necessary to have any therapeutic effect in the absence of any heating, stenosis or pre-coagulation of the vessel by yellow-green pulse 40, but has sufficient fluence to complete the coagulation once yellow green-pulse 40 triggers

10   one or more of these effects.

Referring now to FIG. 6, one preferred embodiment 50 of apparatus for simultaneously or sequentially delivering yellow-green and NIR radiation pulses in accordance with the present invention includes a yellow green laser 52 and an NIR laser 54. Laser 52 may be any pulsed

15   laser which delivers radiation in the spectral range from about 488 nm to 600 nm. Preferably, the lasers include control arrangements not shown for varying output parameters thereof such as pulse duration and fluence. By way of example, suitable lasers for laser 52 include but are not limited to argon lasers, dye lasers, and frequency doubled solid-state

20   lasers such as frequency doubled Nd:YAG or Nd:YVO$_4$ lasers. Laser 54 may be any pulsed laser which delivers radiation in the spectral range from about 605 to 1350 nm. By way of example, suitable lasers include but are not limited to ruby lasers, alexandrite lasers, Nd:YAG lasers, Nd:YVO$_4$ lasers and semiconductor lasers (diode-lasers), or arrays

25   thereof.

The lasers are fired by operating a single footswitch 56. Footswitch 56 is connected to a pulse sequencer 57 which determines the order of firing of the lasers and the interval between firings. Methods of synchronizing firing of separate lasers are well known to those skilled in

30   the art and accordingly are not described in detail herein.

-14-

Laser pulses from lasers 52 and 54 are transported by optical fibers 58 and 60 respectively to handpieces 64 and 62 respectively. Handpieces 62 and 64 include focussing optics and the like (not shown) for focusing or adjusting the spot size of beams delivered thereby.

5   Handpieces 62 and 64 are held by a bracket 66 at an angle to each other. This angle is selected such that beams delivered thereby penetrate skin 69 of a patient being treated and intersect at a point 70 which is arranged to coincident with a vessel to be treated.

Referring now to FIG. 7, another preferred embodiment 80 of
10   apparatus for simultaneously or sequentially delivering yellow-green and NIR radiation pulses in accordance with the present invention is depicted. Apparatus 80 is similar to apparatus 50 inasmuch as it includes yellow-green and NIR lasers 52 and 54 fired in a predetermined sequence with pulses being transported from the lasers by optical fibers 58 and 60.

15   Apparatus 80, however, includes a composite handpiece 82 including optical systems 84 and 86 connected to optical fibers 60 and 58 respectively. Optical system 86 directs a pulse received via optical fiber 58 along a path indicated by single arrows 87 to a turning mirror 88. Turning mirror 88 redirects path 87 to a dichroic mirror 90 which is
20   reflective for the yellow-green radiation and transmissive for the NIR radiation. Dichroic mirror 90 is arranged to combine path 87 with the path (indicated by double arrows 92) of a NIR-radiation pulse delivered from optical system 84 after being received thereby along optical fiber 60.

25   The combined paths 87 and 92 traverse a cooled, transparent window or chill-tip 94 which can be placed on skin 69 of a patient above a vessel at point 70 to be treated. The form and function of chill tips for cooling a patients skin during treatment are well known in the art. Accordingly a detailed description of such a chill tip is not presented
30   herein.

-15-

        Referring now to FIG. 8, yet another preferred embodiment 100 of

apparatus for simultaneously or sequentially delivering yellow-green and

NIR radiation pulses in accordance with the present invention is depicted.

Apparatus 100 includes yellow-green and NIR lasers as 58 and 60

5   described above. Radiation from yellow-green laser 52 travels along a

path 102 via a fold mirror 104 to a dichroic beam combiner 106. At

beam combiner 106 the yellow-green radiation is directed along a

common (collinear) path 108 with NIR radiation from NIR laser 54.

        The yellow-green and NIR radiation is focussed by a lens 110 into

10   a common transport fiber 61. Optical fiber 61 is coupled to a handpiece

83, wherein an optical system 85 directs the yellow-green and NIR

radiation along a common path 114, through a chill tip 94, to blood

vessel 70. Apparatus 100, accordingly allows for a more compact

handpiece than apparatus 80, while still providing a collinear path to

15   blood vessel 70 for the yellow-green and NIR radiation.

        It would also be possible to create a single laser capable of

generating both yellow-green light and NIR light. For example, a Nd:YAG

laser generating light at 1060 nm could be used to generate the NIR

pulses. In order to obtain the yellow-green light, the infrared beam from

20   the Nd:YAG laser could be sent through a doubling crystal located either

inside or outside the resonator. Some form of shutter could be used to

select between the two different wavelength outputs.

        The inventive treatment method was investigated in a series of

tests on blood vessels (venules and arterioles) in the dorsal skin of rats

25   and Syrian golden hamsters. A flap of the animals' dorsal skin was drawn

outward and held by clamps. A 1.0 cm diameter disc was excised from

one fold of the flap, thereby exposing vessels in the sub-dermal region of

the other side of the flap for irradiation. The exposed region was

protected with a window while not being irradiated. The window was

30   removed before irradiations were performed, and the exposed tissue was

-16-

irrigated with isotonic saline solution to prevent dehydration. During

irradiation, the animals were anesthetized with xylazine/ketamine in a

ratio of 3:4 and a concentration of 0.1 milliliters (ml) per 100 grams (g).

A Coherent® VersaPulse® cosmetic laser (VPC^{tm}) was used to

5   provide yellow-green pulses (laser 52). This laser is a frequency-doubled

Nd:YAG laser providing pulses at a wavelength of 532 nm. Handpiece 64

was a Coherent® VersaSpot-F^{tm} adjustable handpiece with a 3.0 mm

spot size. The laser could operate at up to 16 J/cm2 with a pulse

duration of 10.0 ms. An Equilasers EDW-15^{tm} 1064 nm (Nd:YAG) laser

10   was used to provide NIR pulses (laser 54). This laser could be configured

to deliver pulses having a predetermined duration from 0.1 to 10.0 ms,

with pulse energies up to 10.0 Joules. The output of the laser was

collimated by simple telescope optics in handpiece 64 and arranged to

bring the laser output to a 3.0 mm diameter spot coincident with that of

15   laser 52. Mode scramblers on both lasers ensured that the delivered

spots had "top-hat" beam profiles, simplifying radiant exposure

calculations. Laser pulse energies were measured with a power meter.

Pulse-sequence timing was measured with an oscilloscope. Physical

observation of effects of the treatment were made via a CCD video

20   camera from the same side of the flap as irradiations were made.

The effects of individual pulses were ascertained in a separate

series of experiments. For 532 nm pulses only, radiant exposures of 6.0

J/cm^2 were sufficient to produce temporary stenosis of venules on the

order of 170 µm diameter and arterioles on the order of 70 µm diameter.

25   After twenty-four hours, these vessels returned to a normal condition

with blood flowing. Radiant exposures of 10.0 J/cm^2 were sufficient to

produce permanent damage of venules of 135 to 200 µm diameter and in

arterioles of 50 to 100 µm diameter. These results are comparable to

previously published results by Barton et al. in a paper *"Laser Fluence for*

30   *Permanent Damage of Cutaneous Blood Vessels"*, Photochemistry and

-17-

Photobiology 70, 6, pp. 916-920, (1999). For the 1064 nm laser, radiant exposures of 15.0 J/cm^2 were observed to have no effect on vessels of 50 to 100 μm in diameter, while radiant exposures of 42.5 J/cm^2 caused permanent damage of arterioles on the order of 150 μm in diameter and ·

5   venules of 200 μm in diameter.

Next, a series of experiments were performed in which irradiation by a 532 nm pulse having a duration of between about 5.0 and 7.0 ms was followed by a irradiation by 1064 nm pulse having a duration of about 5.0 ms. In each case, there was a delay of 1.0 ms between the

10   falling edge of the 532 nm pulse and the rising edge of the 1064 nm pulse.

The results of this series of experiments are summarized graphically in FIG. 9. Here, curves G and H indicate the 532 nm fluence which provides a 50% probability of permanent venule (curve G) and

15   arteriole (curve H) damage as a function of vessel diameter. These curves are drawn from previously published data (above-referenced Barton et al. paper) on the effects of 532 nm pulses only. As noted above, the 1064 μm fluence required to cause permanent damage of arterioles on the order of 150 μm in diameter and venules of 200 μm in

20   diameter was determined to be 42.5 J/cm^2.

Diamonds 100 indicate the fluence of a 532 nm pulse which in combination with a 1064 nm pulse of duration 5.0 ms and having a fluence of 15.0 J/cm^2 caused permanent arteriole damage. Squares 102 indicate the fluence of a 532 nm pulse which in combination with a 1064

25   nm pulse of duration 5.0 ms and having a fluence of 15.0 J/cm^2 caused permanent venule damage. Inverted triangles 104 indicate the fluence of a 532 nm pulse which in combination with a 1064 nm pulse of duration · 5.0 ms and having a fluence of 30.0 J/cm^2 caused permanent arteriole damage. Triangles 106 indicate the fluence of a 532 nm pulse which in

-18-

combination with a 1064 nm pulse of duration 5.0 ms and having a fluence of 30.0 J/cm^2 caused permanent venule damage.

It can be seen, in general, that the 15.0 and 30.0 J/cm^2 pulses at 1064 nm were about equally effective. Clearly, the lower value would be
5 preferred in a treatment to reduce the possibility of pain being felt. It can be seen, in particular, that for a particular vessel of a particular diameter, the 532 nm and 1064 nm fluences required to cause permanent damage are respectively about one-half and one-third those that would be required for 532 nm and 1064 nm pulses alone. This
10 indicates that the treatment method of the present invention may have a significantly reduced possibility of epidermal damage and other above-discussed side effects compared with prior-art treatments using individual pulses at only one or the other wavelength.

The method of the present invention is discussed above primarily
15 with reference to delivering a single pulse of yellow-green radiation followed by a single pulse of NIR radiation. The above-discussed experimental results appear to confirm the effectiveness of this delivery scheme in reducing total fluence required. However, while this delivery scheme is preferred scheme, it should not be considered as limiting. A
20 brief discussion of other possible delivery schemes is set forth below with reference to FIGS 10A, 10B and 10C.

FIG. 10A schematically depicts two pulses 40 of yellow-green radiation being delivered followed by two pulses 42 of NIR radiation. FIG. 10B schematically depicts a pulse 42 of NIR radiation being
25 delivered and a pulse 40 of yellow-green radiation being delivered while radiation is still being delivered by the pulse 42. A second pulse 42 of NIR radiation may be used to complete coagulation. FIG. 10C schematically depicts two pulses 40 of yellow green radiation being delivered with a pulse 42 of NIR radiation being delivered partially
30 concurrent with and following delivery of the last pulse 42. It is

preferable that any sequence of pulses delivered in lieu of a single pulse collectively has a lower fluence than would be necessary to complete coagulation. These and similar radiation delivery schemes may be practiced by those skilled in the art without departing from the spirit and

5   scope of the present invention.

In summary, a method of treating vascular disorders is described above in which a blood vessel is treated by delivering electromagnetic radiation thereto having a wavelength in a range between about 480 nm and 600 nm, and, within a selected time period following initiation of this

10   delivery, delivering electromagnetic radiation thereto having a wavelength in a range between about 605 nm and 1350 nm. The delivery of the shorter and longer wavelength radiations may be at least partially concurrent. The shorter wavelength radiation conditions the blood vessel for complete coagulation of blood therein by the longer

15   wavelength radiation. As evident from the above-presented results, fluences required to cause permanent damage are respectively about one-half or less and one-third or less than those that would be required using respectively the shorter and longer wavelengths alone.

Conditioning by the shorter wavelength radiation reduces the total

20   radiation fluence at the longer wavelength required to complete coagulation of blood in the vessel. Any one or more of three possible factors may contribute to the conditioning. The first possible factor is a stenosis or shrinking of the vessel. The second possible factor is a pre-coagulation of blood in the vessel, which can take the form of a clot of

25   coagulated blood (coagulum) in the vessel. The third possible factor is the heating or photochemical modification of the blood in the vessel by the shorter wavelength pulse or pulses.

The first and second factors, alone or in combination, contribute to reducing the volume of blood to be coagulated. This proportionately

30   reduces the fluence at the second wavelength compared with that which

-20-

would be necessary to complete coagulation in the absence of the
volume reduction.

The second and third factors, alone or in combination, can
contribute to increasing the efficiency of coagulation of blood in the
5   preconditioned vessel by the longer wavelength radiation. Any one or
both of two effects can contribute to this increased efficiency. The first
effect is a preheating of the blood by the shorter wavelength radiation.
This is effective in itself inasmuch as less of the longer wavelength
radiation is required to raise the temperature of blood in the vessel to the
10   coagulation temperature. The second effect is an increased absorption of
the longer wavelength radiation in heated or photochemically modified
blood compared with unheated blood.

In selecting a time interval for delivering the longer wavelength
radiation relative to delivery of the shorter wavelength radiation the
15   following should be considered. Stenosis (shrinkage) occurs essentially
instantaneously, but the stenosed condition of the blood vessel will return
to a normal condition in a period from about one to twenty-four hours or
more if another pulse or radiation of any wavelength is not delivered to
the vessel. A clot (coagulum) resulting from the delivery of the shorter
20   wavelength radiation will be cleared by blood flow through the vessel in a
period ranging from a few hundred milliseconds to a minute or more,
depending on vessel size. Cooling of preheated blood occurs in a time
period from about tens of milliseconds to a second or more, dependent
on blood vessel diameter as discussed-above.

25   Clearly, in order to benefit from all of the above discussed
preconditioning factors and effects, the time interval between delivery of
the shorter and longer wavelengths must be short enough to take
advantage of the thermal effects and is accordingly preferably no greater
than about two thermal relaxation times for a targeted blood vessel. A
30   period of up to a few hundred milliseconds could allow one or both of the

-21-

pre-coagulation and volume reduction effects to be effective. A period as long as an hour or more may still provide some synergistic effect from the volume reduction effect alone.

5   The present invention has been described in terms of a preferred and other embodiments. The present invention is not limited, however, to the embodiments described and depicted. Rather, the invention is limited only by the claims appended hereto.

-22-

WHAT IS CLAIMED IS:

1.   A method for treating a vascular disorder, comprising the steps of:
        (a)   conditioning a blood vessel by delivering
electromagnetic radiation having a first wavelength to said blood
vessel; and
        (b)   coagulating blood in said conditioned blood vessel by
delivering electromagnetic radiation having a second wavelength
to said conditioned blood vessel, said second wavelength being
longer than said first wavelength.

2.   The method of claim 1, wherein in step (b) said blood coagulation
causes complete blockage of said blood vessel.

3.   The method of claim 2, wherein said conditioning includes one or
more of (i) causing shrinkage of said blood vessel; (ii) heating blood in said
blood vessel to a temperature above normal blood temperature; and (iii)
causing partial blockage of said blood vessel by partially coagulating blood
therein.

4.   The method of claim 1, wherein said delivery of said second-
wavelength radiation and said resulting complete blockage of said blood
vessel causes permanent damage to said blood vessel.

5.   The method of claim 1, wherein steps (a) and (b) are carried out at
least partially concurrently.

-23-

6.   The method of claim 1, wherein step (b) is carried out within a
selected time interval following completion of step (b).

5   7.   The method of claim 6, wherein in step (a) said conditioning step
includes heating blood in said blood vessel to a temperature above normal
blood temperature, and step (b) is carried out before said heated blood
cools to said normal blood temperature.

10   8.   The method of claim 6, wherein in step (a) said conditioning step·
includes causing partial blockage of said blood vessel by partially
coagulating blood therein, and step (b) is carried out while said blood
vessel partially blocked by said partial coagulation.

.15 .9.   The method of claim 6, wherein in step (a) said conditioning step·
includes causing shrinkage of said blood vessel, and step (b) is carried out
while said blood vessel is shrunk.

       10.   The method of claim 1, wherein said first- wavelength radiation and
20   said second-wavelength radiation are each delivered in the form of one or
more radiation pulses.

       11.   The method of claim 10, wherein delivery of a said pulse of said
first-wavelength radiation is at least partially concurrent with delivery of a
25   said pulse of said second ·wavelength radiation.

-24-

12.   The method of claim 10, wherein said pulses have a duration of between about 2 and 100 milliseconds.

5   13.   The method of claim 1, wherein said first-wavelength radiation has a fluence between 8 and 30 J/cm^2 and said second wavelength radiation has a fluence between about 10 and 100 J/cm^2.

14.   The method of claim 1, wherein said first wavelength is between

10   about 480 and 600 nanometers and said second wavelength is between about 605 and 1350 nanometers.

15.   The method of claim 14, wherein said first wavelength is about 532 nm and said second wavelength is about 1064 nm.

15

16.   A method for treating a vascular disorder, comprising the steps of;
            (a) irradiating a blood vessel with one or more pulses of electromagnetic radiation having a first wavelength; and
            (b) within a selected time interval after initiating delivery of

20   said one or more first-wavelength pulses, irradiating said blood vessel with one or more pulses of electromagnetic radiation having a second wavelength longer than said first wavelength, said first and second wavelengths and said time interval selected such that said first and second-wavelength pulses cooperatively

25   cause permanent damage to said blood vessel.

-25-

17.   The method of claim 16, wherein if only one of each of said first and second wavelength pulses is delivered, each thereof has a radiation fluence insufficient to individually cause said permanent damage.

5   18.   The method of claim 16, wherein if more than one of each of said first or second wavelength pulses is delivered, said pulses collectively have a radiation fluence insufficient to cause said permanent damage.

19.   The method of claim 16, wherein said first wavelength is between 10   about 480 and 600 nanometers and said second wavelength is between about 605 and 1350 nanometers.

20.   The method of claim 19, wherein said first wavelength is about 532 nanometers and said second wavelength is about 1064 nanometers.

15

21.   The method of claim 16, wherein said one or more first-wavelength pulses collectively have a fluence between about 8 and 30 J/cm^2 and said one or more second-wavelength pulses collectively have a fluence between about 10 and 100 J/cm^2.

20

22.   The method of claim 16, wherein said selected time interval is less than about twice the thermal relaxation time for the blood vessel being treated.

23.   The method of claim 16, wherein at least a portion of at least one of said second wavelength pulses is delivered concurrently with a said first wavelength pulse.

5   24.   A method for treating a vascular disorder, comprising the steps of:
            delivering to a blood vessel a first fluence of
            electromagnetic radiation having a first wavelength and a second
            fluence of electromagnetic radiation having a second wavelength
            longer than said first wavelength, and wherein said fluences are
10   delivered in a manner such that the delivered fluences cause
            permanent damage to said blood vessel.

25.   The method of claim 24, wherein said delivery of said first fluence to said blood vessel causes one of more of shrinkage of said blood vessel,
15   heating of blood in said blood vessel to a temperature above normal blood temperature, and partial blockage of said blood vessel by partially coagulating blood therein.

26.   The method of claim 25, wherein said second fluence causes
20   complete coagulation of blood in said blood vessel.

27.   The method of claim 26, wherein said first fluence alone is not sufficient not cause complete coagulation of blood in said blood vessel.

25   28.   The method of claim 27, wherein said second fluence alone is not sufficient not cause complete coagulation of blood in said blood vessel.

-27-

29. A method for treating a vascular disorder, comprising the steps of:

(a) delivering a first pulse of electromagnetic radiation having a wavelength between about 480 nanometers and 600

5   nanometers to a blood vessel; and

(b) delivering a second pulse of electromagnetic radiation having a wavelength between about 605 nanometers and 1350 nanometers to the blood vessel, with the parameters and timing of delivery of said first and second pulses being selected such

10   that said first and second pulses cooperatively cause permanent damage to said blood vessel.

30. The method of claim 29, wherein the fluence in said first pulse is insufficient to cause damage in the absence of said second pulse.

15

31. The method of claim 30, wherein the fluence in said second pulse is insufficient to cause damage in the absence of said first pulse.

32. The method of claim 29, wherein at least portions of said first and

20   second pulses are delivered concurrently.

33. The method of claim 32, wherein said second pulse is delivered within a selected time interval after the delivery of said first pulse.

-28-

34.   The method of claim 29, wherein said first pulse has a wavelength of about 532 nm and said second pulse has a wavelength of about 1064 nm.

5   35.   The method of claim 34, wherein said first pulse has a duration between about 2 and 100 milliseconds and said second pulse has a duration between about 2 and 100 milliseconds.

36.   The method of claim 34, wherein said first pulse has a fluence
10   between about 8 and 30 J/cm^2 and said second pulse has a fluence between about 10 and 100 J/cm^2.

37.   Apparatus for treating vascular disorders, comprising:
       a first light-source for delivering electromagnetic radiation
15   having a first wavelength;
       a second light-source for delivering electromagnetic radiation having a second wavelength, said second wavelength being longer than said first wavelength;
       a control arrangement for controlling the fluence of said
20   electromagnetic radiation delivered by each of said first and second sources, said control arrangement including a sequencer for timing activation of any one of said first and second sources relative to activation of the other; and
       an optical arrangement for delivering said electromagnetic
25   radiation from each of said first and second light-sources to one particular region of a blood vessel being treated.

-29-

38.   A method as recited in claim 6, wherein the selected time interval is between 2 and 100 milliseconds.

39.   A method as recited in claim 16, wherein the selected time interval is between 2 and 100 milliseconds.

5   40.   A method a recited in claim 33, wherein the selected time interval is between 2 and 100 milliseconds.
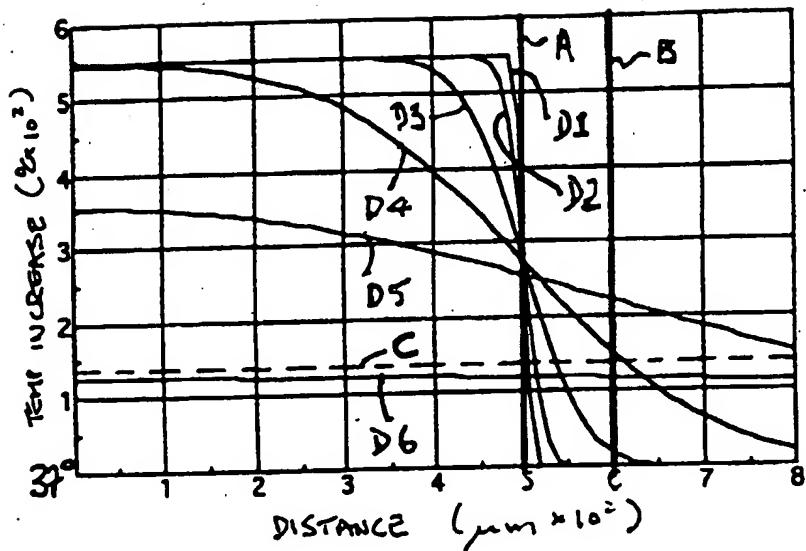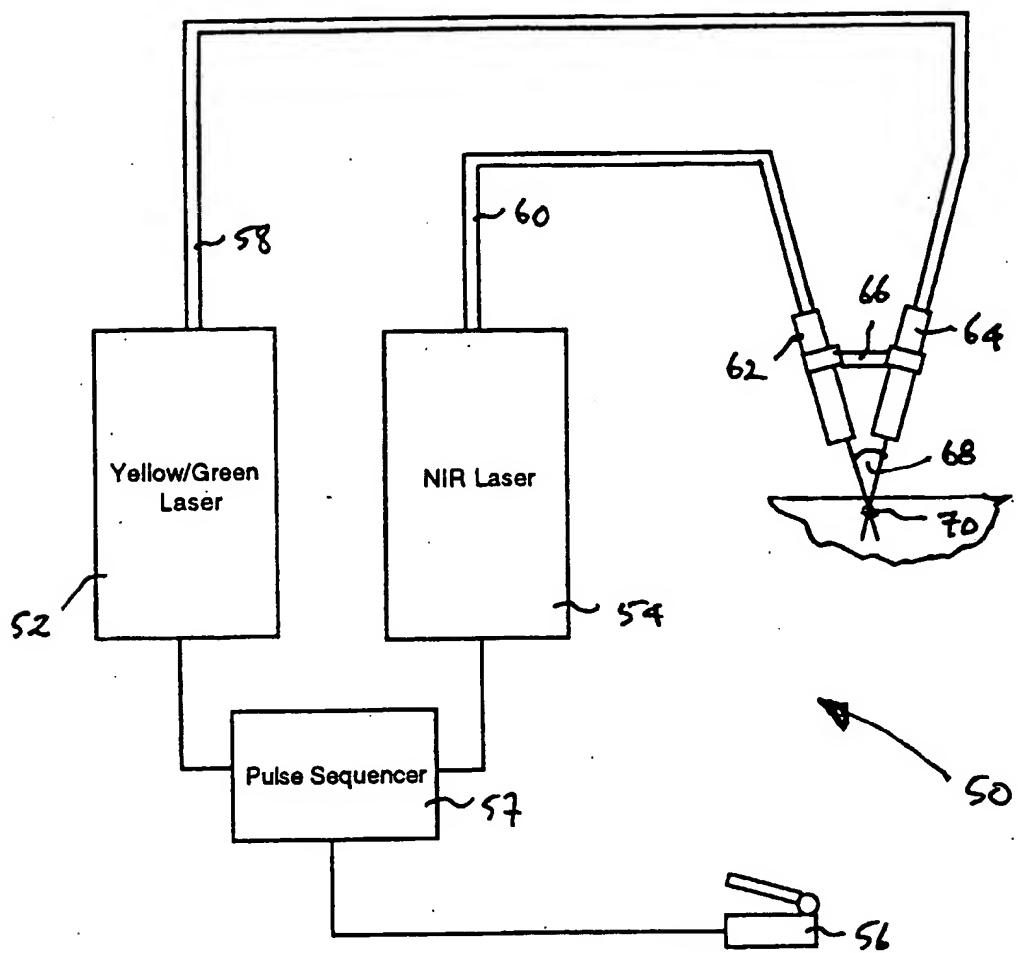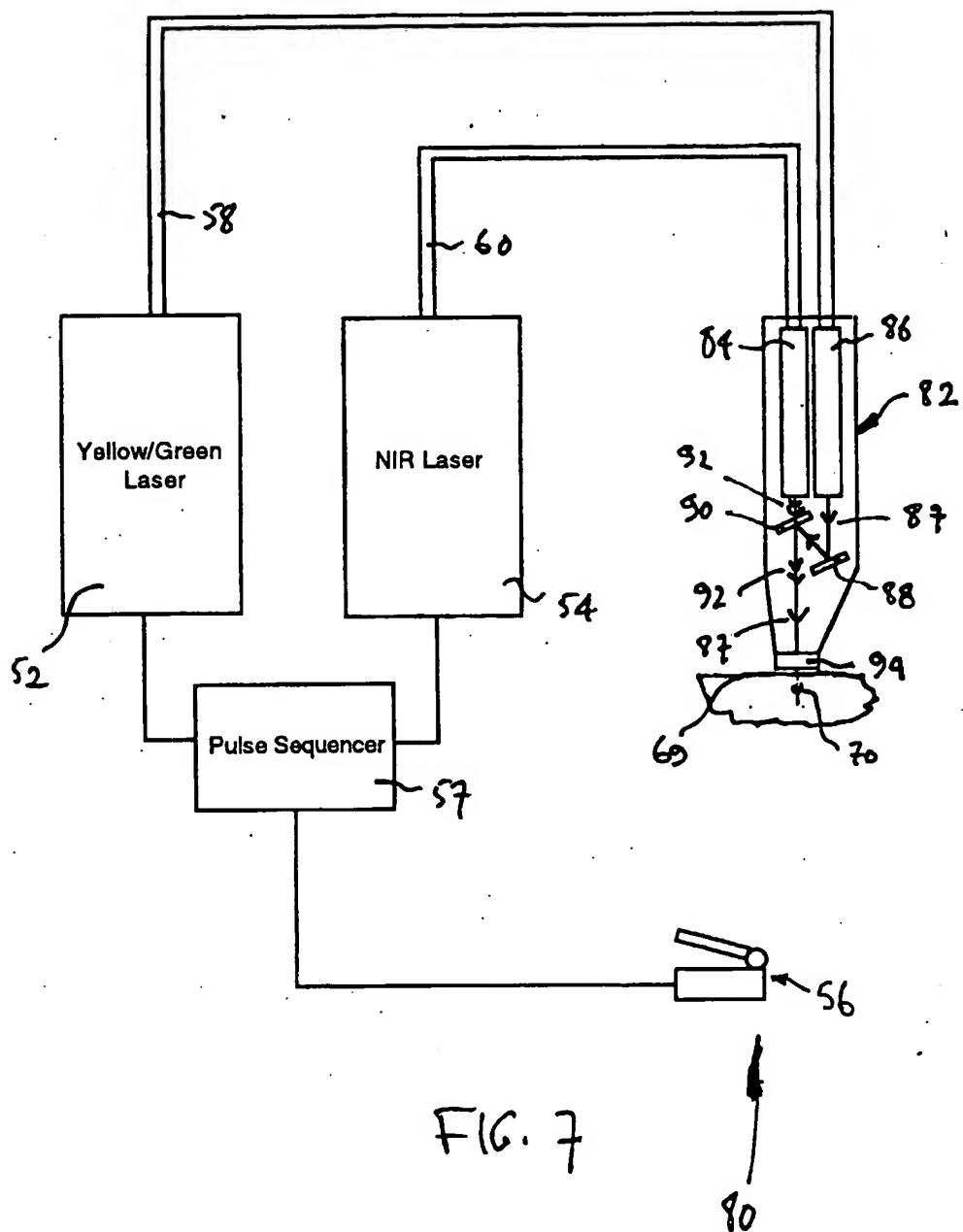
FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5A

FIG. 5B

FIG. 5C
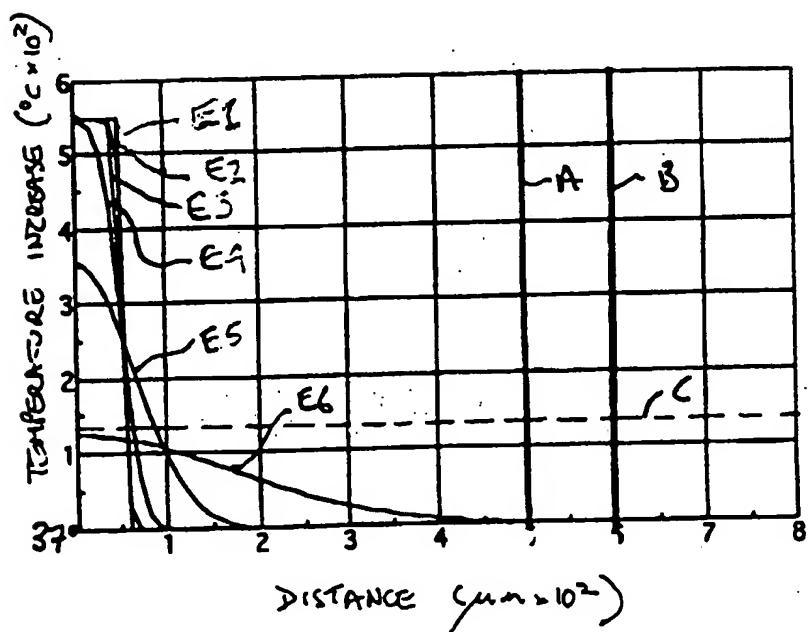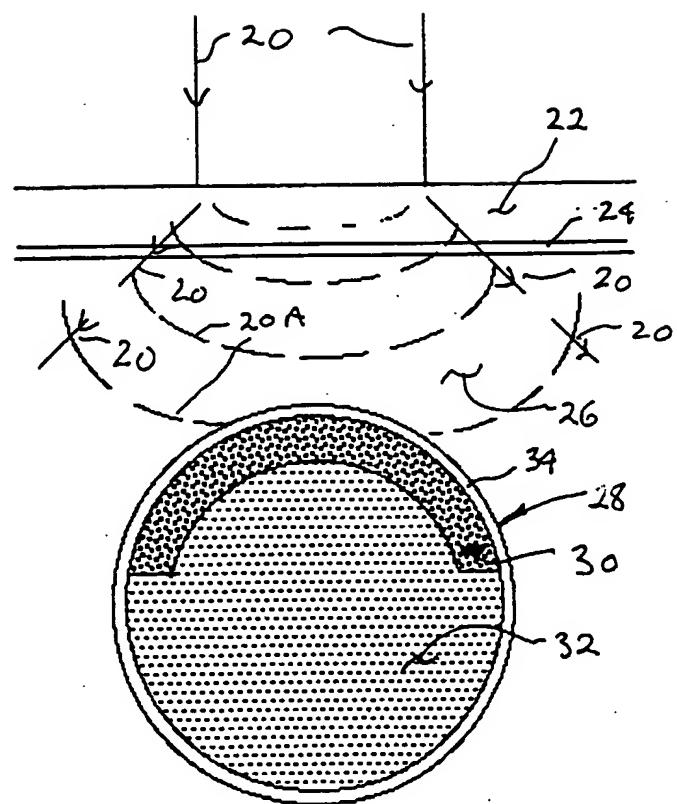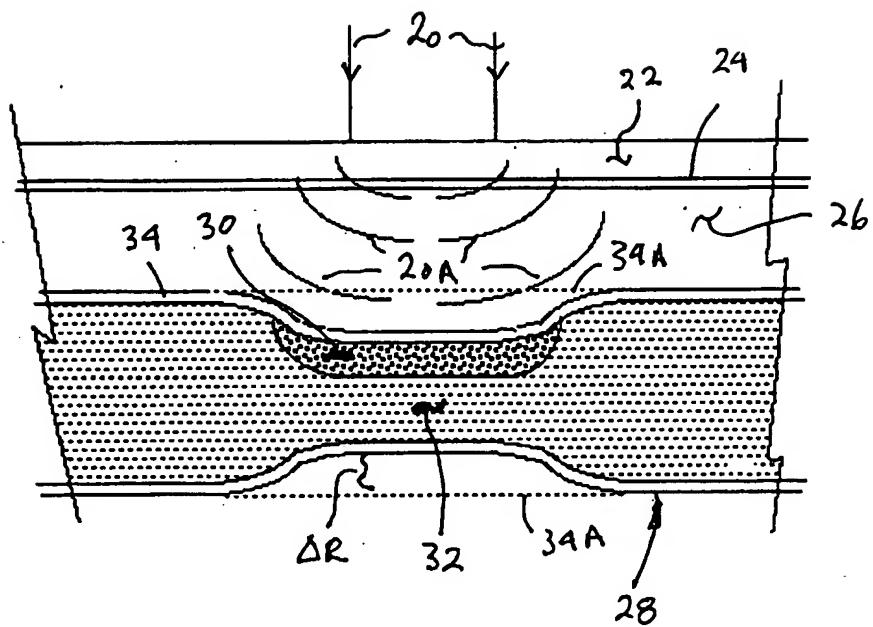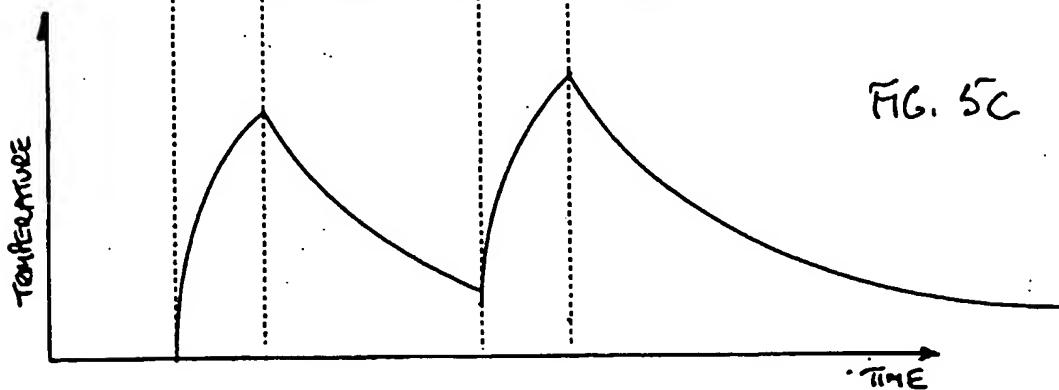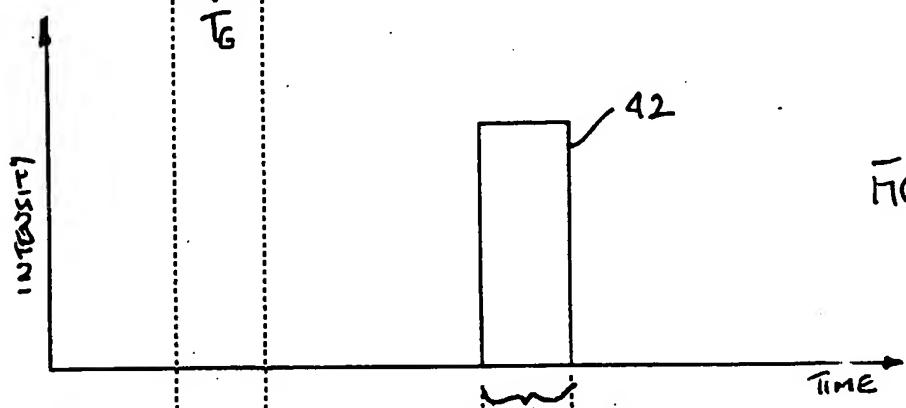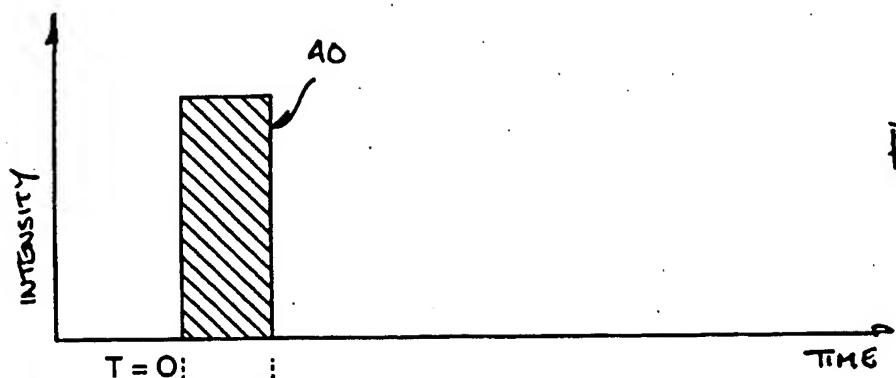
FIG. 6

FIG. 7
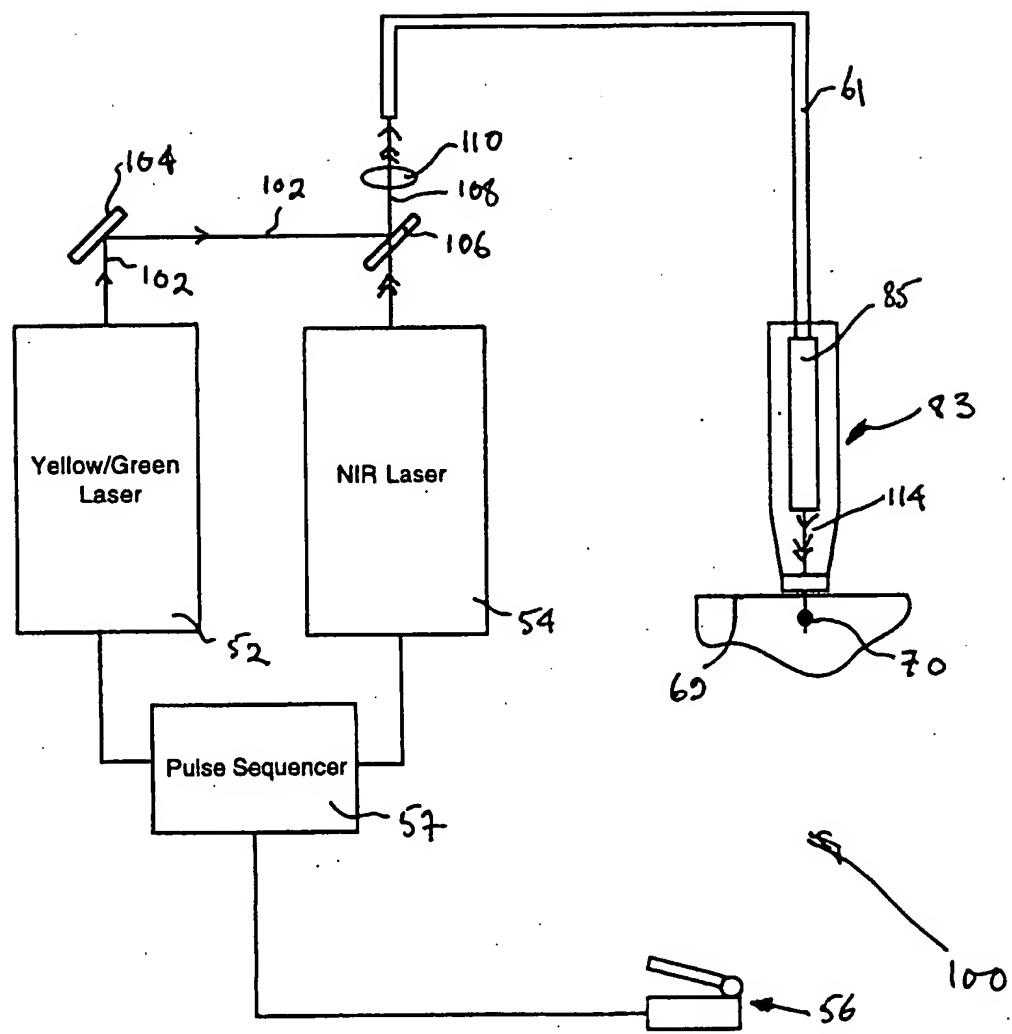
FIG. 8
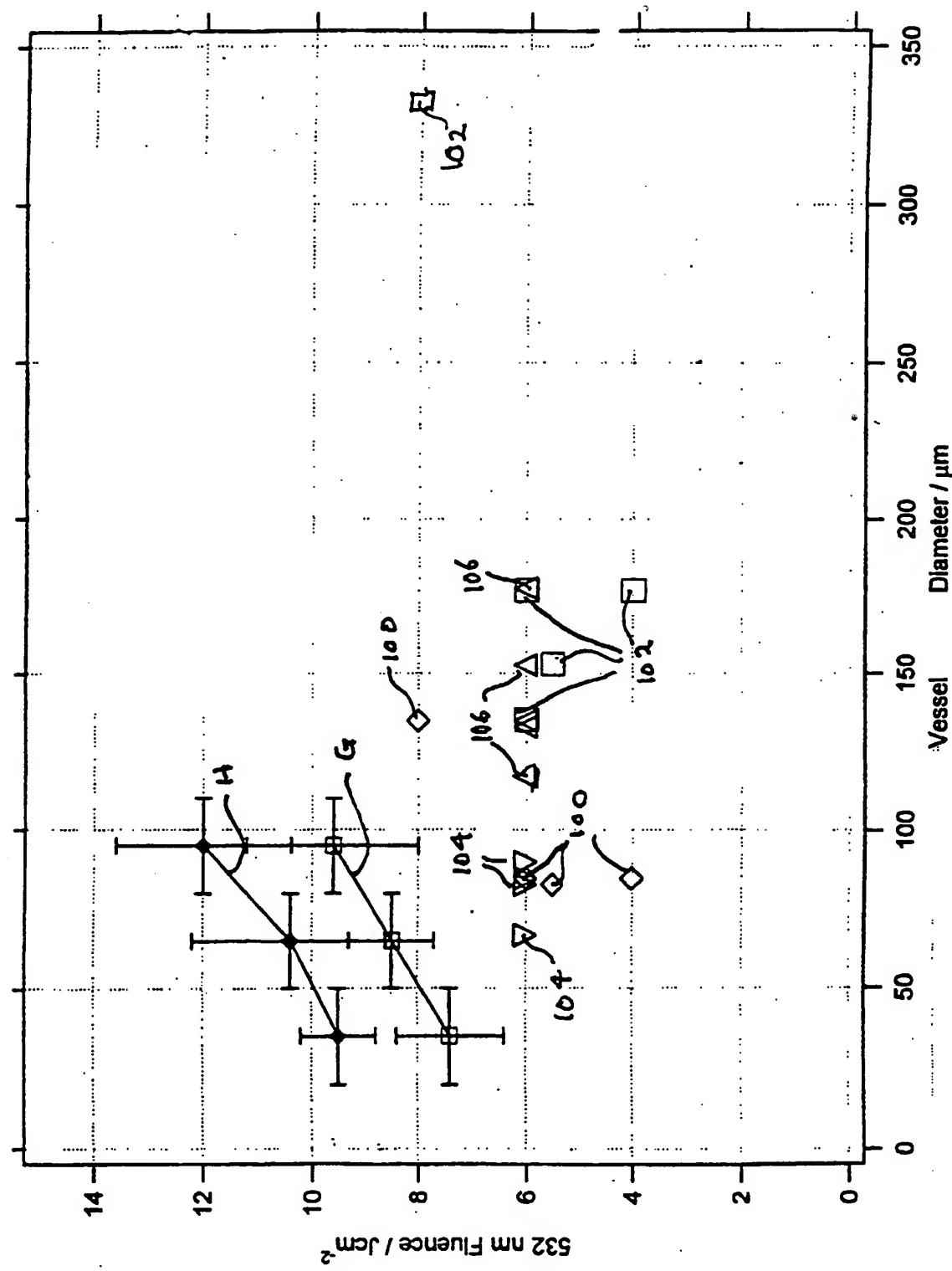
FIG. 9
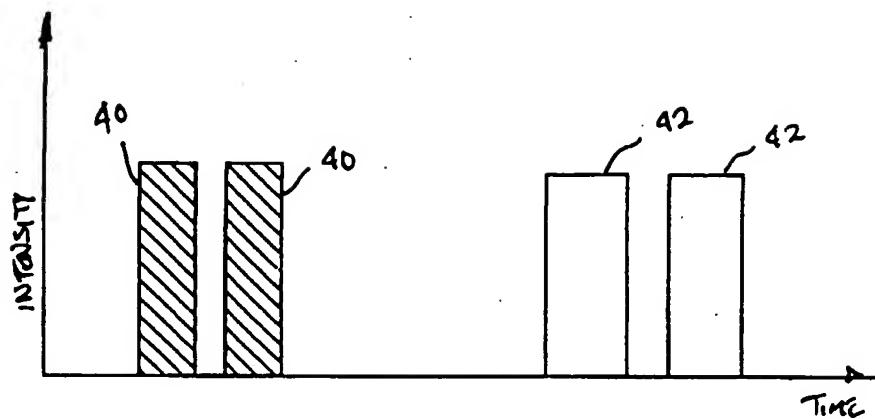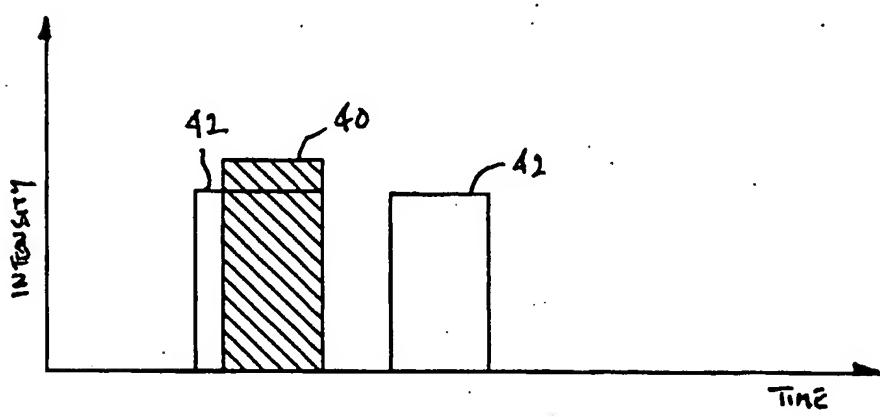
FIG. 10A

FIG. 10B
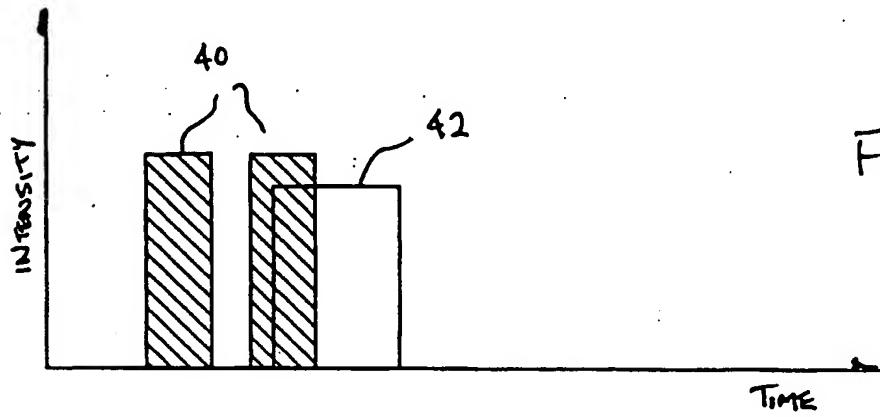
FIG. 10C

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7   A61B18/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7   A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 312 396 A (FELD MICHAEL S ET AL) 17 May 1994 (1994-05-17) claim 8	37
A	US 5 662 644 A (SWOR WILLIAM T) 2 September 1997 (1997-09-02) abstract	37
A	US 4 573 465 A (SUGIYAMA SEIJI ET AL) 4 March 1986 (1986-03-04) abstract; figure 1	37
A	WO 91 13652 A (CANDELA LASER CORP) 19 September 1991 (1991-09-19) abstract; figure 5	37
	-/--	

X	Further documents are listed in the continuation of box C.	X	Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2001	27/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mayer, E

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 6 149 645 A (TOBINICK EDWARD L) 21 November 2000 (2000-11-21) abstract -----	37

INTERNATIONAL SEARCH REPORT

Information on patent family members

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5312396	A	17-05-1994	WO	9203977 A2	19-03-1992
US 5662644	A	02-09-1997	WO	9743008 A1	20-11-1997
US 4573465	A	04-03-1986	JP	58086787 A	24-05-1983
			CA	1195737 A1	22-10-1985
			DE	3242612 A1	26-05-1983
WO 9113652	A	19-09-1991	AU	7463991 A	10-10-1991
			AU	7562591 A	10-10-1991
			DE	69103409 D1	15-09-1994
			DE	69103409 T2	23-03-1995
			EP	0519964 A1	30-12-1992
			WO	9113652 A1	19-09-1991
			WO	9113653 A1	19-09-1991
			US	5312395 A	17-05-1994
US 6149645	A	21-11-2000	NONE		